

restaging strategy,<sup>4</sup> with the goal of avoiding additional total mesorectal excision.

Defining the optimal primary endpoint is challenging because of variation in opinion between patients, clinicians, and regulatory agencies.<sup>5</sup> This challenge is even more relevant when the prognosis of cancer is good, as expected in good responders, and quality of life becomes a priority. Therefore, we proposed a composite endpoint including both oncological and non-oncological outcomes. We agree that absence of weighting in the composite endpoint makes interpretation difficult. However, we analysed each component separately as secondary endpoints to facilitate interpretation. Weighting each outcome of the composite endpoint does not necessarily facilitate interpretation, because weighting is prone to judgment calls. We also agree that GRECCAR2 was designed as a superiority trial and not powered to conclude for a non-inferiority hypothesis. Such a non-inferiority trial would require 1000 patients because of the low incidence of excellent responders.

We agree that the terminology per-protocol analysis, which is more familiar to clinicians, should be replaced by as-treated analysis,<sup>6</sup> which is more appropriate and corresponds with our statistical analyses. This complementary analysis should be seen as a secondary and non-randomised comparison, and did not change the results of the study.

We declare no competing interests.

\*Eric Rullier, Véronique Vendrely, Quentin Denost, Julien Asselineau, Adélaïde Doussau  
eric.rullier@chu-bordeaux.fr

Departments of Colorectal Surgery (ER, QD) and Radiotherapy (VV), Haut-Lévêque Hospital, CHU Bordeaux, Université de Bordeaux, Pessac 33600, France; and Unité de Soutien Méthodologique à la Recherche Clinique et Epidémiologique du CHU de Bordeaux, Université Bordeaux, Bordeaux, France (JA, AD)

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## Pitfalls of the healthy vaccinee effect

We read with interest the Article by Helen Petousis-Harris and colleagues (Sept 30, 2017, p 1603),<sup>1</sup> which showed that the vaccine against outer membrane vesicle meningococcal B was 31% effective in reducing gonorrhoea among attendees of 11 clinics in New Zealand for patients with sexually transmitted infections. We disagree, however, with the authors' claims that their "findings provide experimental evidence that these vaccines could offer moderate cross-protection against [gonorrhoea]".

First, theirs was a non-experimental (observational) retrospective study in clinical research, in which efficacy claims require robust evidence from well conducted randomised controlled trials. Second, their findings are not robust, even by the standards of observational studies: use of patients with chlamydia as controls could have reduced the bias associated with differences in access to health care, but it probably did not lessen the effects of more pernicious confounders, such as the differences in lifestyle and behaviour between vaccinated and unvaccinated people.<sup>2</sup> Even among clinic attendees, chlamydia, which is often asymptomatic and only discovered on routine screening,

might not be a suitable control condition for gonorrhoea, which is often associated with riskier sexual behaviour.<sup>3</sup> Gonorrhoea circulates in focused outbreaks among high-risk groups. Chlamydia is more egalitarian, affecting young people of all backgrounds.<sup>4,5</sup> We suspect that their control group was dominated by more health-conscious people with potentially higher vaccine uptake. If true, one would expect vaccines other than outer membrane vesicle meningococcal B vaccine to share the same protective effect. Our hypothesis can be tested in a sensitivity analysis by estimating the effectiveness of other vaccines, such as those against human papilloma virus or hepatitis B.

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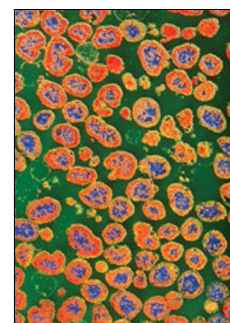
\*Salaheddin M Mahmud,  
Christiaan H Righolt  
salah.mahmud@gmail.com

Vaccine and Drug Evaluation Centre, University of Manitoba, Winnipeg, MB R3E 0T5, Canada

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## Authors' reply

In our Article,<sup>1</sup> we presented findings from a case-control study that showed a protective effect of a meningococcal vaccine against gonorrhoea infection. In their Correspondence, Salaheddin Mahmud and Christiaan Righolt argue



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that the correct method to determine vaccine efficacy is a randomised controlled trial (RCT) and that our use of chlamydia as a control is problematic. We would like to clarify the points raised in their letter.

First, we agree with Mahmud and Righolt that vaccine efficacy is best assessed using RCTs. However, our study is on vaccine effectiveness, which is normally assessed using observational methods such as case-control and cohort designs.<sup>2</sup>

Second, we agree that if participation in chlamydia screening was associated with greater health literacy and was also associated with greater vaccine use, then the vaccine would appear effective because of this unmeasured confounding. However, any unmeasured differences in risk between infection with chlamydia and with gonorrhoea are only of concern in this study if the study groups (ie, high risk for gonorrhoea vs high risk for chlamydia) confer large differences in likelihood of vaccination. People with greater wealth and health literacy are more likely to access primary health care in New Zealand, and the user fee-for-service in primary care is a recognised barrier for people with low incomes. By contrast, New Zealand's publicly funded sexual health clinics (where this study was done) have always been free, which is more likely to have biased our study population towards attendees from a low socioeconomic background. The programme to vaccinate people in New Zealand with an outer membrane vesicle meningococcal B vaccine was notably successful in reaching high deprivation populations (which was part of the programme strategy). There were no socioeconomic inequities in the uptake of this vaccine because of the way that the mass campaign was delivered; therefore, in this case, groups at highest risk of gonorrhoea were equally, or slightly more likely, to be vaccinated. Furthermore, our analyses adjusted for ethnicity and deprivation.

Third, we tested the effect of changes to the case and control groups by varying the definition of cases to include people who were co-infected with chlamydia and gonorrhoea or, alternatively, excluding them as cases and including them as controls instead.

Finally, sexual health clinics in New Zealand routinely offer testing for all sexually transmitted infections, not selected infections as might occur in a chlamydia screening programme, so this should not introduce bias between selection of cases and controls.

We acknowledge that the most rigorous way to establish efficacy of a vaccine is through an RCT. We did an effectiveness study with robust findings to suggest that this vaccine had a protective effect against gonorrhoea. We believe that our study provides evidence to support conduct of an RCT.

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*\*Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Felicity Goodyear-Smith, Steven Black*  
h.petousis-harris@auckland.ac.nz

Department of Primary Health Care (HP-H, JP, FG-S) and Department of Community Health (PS), University of Auckland, Auckland 1072, New Zealand; Sexual Health Services, Waikato District Health Board, Hamilton, New Zealand (JM); and Department of Pediatrics, Global Health Center, Cincinnati Children's Hospital, Cincinnati, OH, USA (SB)

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## Department of Error

Kande Betu Ku Mesu V, Mutombo Kalonji W, Bardonneau C, et al. Oral fexinidazole for late-stage African *Trypanosoma brucei* gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. *Lancet* 2017; **391**:144–54—In this Article (published online first on Nov 4, 2017), the route of administration of nifurtimox eflornithine combination therapy was corrected in the Background section in the Summary. This correction was made to the online version as of Nov 9, 2017, and the printed Article is correct.